

PCT/GB 2000

10/512138
001795



INVESTOR IN PEOPLE

PRIORITY DOCUMENT

SUBMITTED OR TRANSMITTED IN
COMPLIANCE WITH RULE 17.1(a) OR (b)

The Patent Office
Concept House
Cardiff Road
Newport

South Wales 21 MAY 2003
NP10 8QQ

WIPO PCT

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

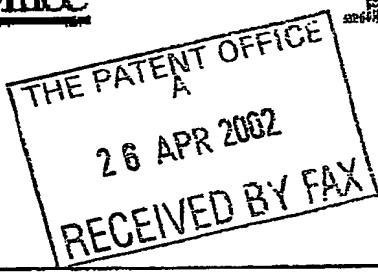
Signed

Dated 9 May 2003

**The
Patent
Office**

Request for grant of a patent

(Write on the back of this form. You can also get statutory forms from the Patent Office to help with this form.)



The Patent Office
Cardiff Road
Newport
Gwent NP9 1RH

Your reference

SMC 60512/GB/PI

Patent application number: **26 APR 2002** **0209539.6**

1 name, address and postcode of the or of
the applicant (underline all surnames)

Avecla Limited
Hexagon House
Blackley
Manchester, M9 8ZS
United Kingdom

26APR02 E714147-1 D02944
P01/7700 0.00-0209539.6

2ents ADP number (if you know it)

07764137001

3the applicant is a corporate body, give the
country/state of its incorporation

GB

4use of the invention

MONOMER, POLYMER AND PROCESS

5name of your agent (if you have one)

GAIRNS, Raymond Stevenson

6address for service* in the United Kingdom
which all correspondence should be sent
(including the postcode)

Avecla Limited
Hexagon House
Blackley
Manchester, M9 8ZS
United Kingdom

7ents ADP number (if you know it)

01071976004

8you are declaring priority from one or more
earlier patent applications, give the country
of the date of filing of the or of each of these
earlier applications and (if you know it) the or
ch application number

Country	Priority application number (if you know it)	Date of filing (day / month / year)
---------	---	--

9his application is divided or otherwise
derived from an earlier UK application,
give the number and the filing date of
the earlier application

Number of earlier application

Date of filing (day / month / year)
--

10a statement of inventorship and of right
to grant of a patent required in support of
this request? (Answer 'Yes' if

any applicant named in part 3 is not an inventor, or
there is an inventor who is not named as an
applicant, or
any named applicant is a corporate body
or note (10)

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document.

Continuation sheets of this form

Description

7

Claim(s)

1

Abstract

Drawing(s)

10. If you are also filing any of the following, state how many against each item.

Priority documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (Patents Form 7/77)

Request for preliminary examination and search (Patents Form 9/77)

Request for substantive examination (Patents Form 10/77)

Any other documents
(Please specify)

11.

I/We request the grant of a patent on the basis of this application.

Signature

Date 26/4/77

Aveda Limited Authorised Signatory

12. Name and daytime telephone number of person to contact in the United Kingdom

Mrs K.M. Pinder/Miss G. Terry 0161 721 1361/2

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

- If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.
- Write your answers in capital letters using black ink or you may type them.
- If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.
- If you have answered 'Yes' Patents Form 7/77 will need to be filed.
- Once you have filled in the form you must remember to sign and date it.
- For details of the fee and ways to pay please contact the Patent Office.

APPLICANTS

AVECIA Limited

TITLE

MONOMER, POLYMER AND PROCESS

MONOMER, POLYMER AND PROCESS

The present invention relates to a process for the synthesis of polymers which are useful as supports in solid phase organic synthesis (SPOS) and to intermediates for use therein.

5 PCT/GB99/02193 discloses a series of novel polymer resin supports which find use as supports in solid phase organic synthesis (SPOS).

These polymer resins are of commercial importance and there exists a need for improved methods for their synthesis. We have found that certain novel monomers and resins find use in improved routes to these polymers.

10 According to a first aspect of the present invention there is provided a monomer which comprises a protected hydroxypolyC₂₋₄ alkyleneoxy chain attached to a polymerisable unit wherein the protected hydroxypolyC₂₋₄ alkyleneoxy chain contains from 2 to 10 C₂₋₄ alkyleneoxy groups and wherein the hydroxypolyC₂₋₄ alkyleneoxy chain is protected with an optionally substituted trityl group.

15 The hydroxypolyC₂₋₄ alkyleneoxy chains attached to the monomer according to the present invention are often selected from hydroxypolyethyleneoxy (HO(CH₂CH₂O)₂₋₁₀), hydroxypolypropyleneoxy (HO(CH₂CH(CH₃)O)₂₋₁₀) and hydroxypolybutyleneoxy (HO(CH₂CH(C₂H₅)O)₂₋₁₀) chains. In a preferred embodiment of the invention the hydroxypolyC₂₋₄ alkyleneoxy chain is hydroxypolyethyleneoxy.

20 The number of C₂₋₄ alkyleneoxy groups in the hydroxypolyC₂₋₄ alkyleneoxy chain can range from 2 to 10, but is preferably from 2 to 8 and more preferably from 3 to 5. Most preferably, there are four C₂₋₄ alkyleneoxy groups in the hydroxypolyC₂₋₄ alkyleneoxy chain.

25 In a highly preferred embodiment of the invention the hydroxypolyC₂₋₄ alkyleneoxy chain is hydroxytetraethyleneoxy (HO(CH₂CH₂O)₄).

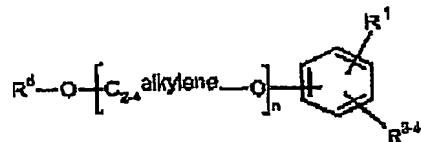
The polymerisable unit of the monomer according to the present invention is often selected from optionally substituted styrenes, acrylates and acrylamides. In a preferred embodiment of the invention the polymerisable unit is an optionally substituted styrene, optionally substituted methylstyrene, optionally substituted ethyl (meth)acrylate, optionally substituted propyl (meth)acrylate or optionally substituted N-methyl (meth)acrylamide.

30 In a highly preferred embodiment of the invention the polymerisable unit is an optionally substituted styrene or optionally substituted methylstyrene.

35 Where the polymerisable unit is an optionally substituted styrene or optionally substituted methylstyrene, the phenyl ring of the styrene is preferably optionally substituted by 1 or 2 substituents often selected from methyl, ethyl, propyl, fluoro, chloro and bromo.

Optionally substituted trityl groups include triphenylmethyl [trityl], di-methoxyphenylphenylmethyl [dimethoxy trityl], methoxyphenyl-di-phenylmethyl [monomethoxy trityl], and 2-chlorophenyldi-phenylmethyl [2-chlorotriityl] groups.

In a most preferred embodiment of the invention, the monomer is a compound of formula (1)



wherein

R^1 is an optionally substituted ethylene group;

R^{24} are independently hydrogen, hydrocarbyl, halogen, or hydrocarboxy;

R^6 is an optionally substituted trityl group; and

n is 2 to 10.

Preferably, R^1 is a $CH=CH_2$, $CH=CHCH_3$, or $C(CH_3)=CH_2$ group. Most preferably, R^1 is a $CH=CH_2$.

Preferably, the $R^6O-[C_{24}\text{alkylene-O-}]_n$ group is para to R^1 .

Preferably, $[-C_{24}\text{alkylene-O-}]_n$ is $[-CH_2CH_2O-]_n$, $[-CH_2CH(CH_3)O-]_n$, or $[-CH_2CH(C_2H_5)O-]_n$. Most preferably $[-CH_2CH_2O-]_n$.

Preferably n is 2 to 8, more preferably n is 3 to 5. Most preferably n is 4.

Preferably R^{24} are all hydrogen.

Hydrocarbyl includes alkyl, aryl, alkaryl and aralkyl groups. Preferable when any of R^{24} are hydrocarbyl or hydrocarboxy groups the hydrocarbyl is an alkyl group, most preferably C_{1-4} alkyl group.

The monomers according to the first aspect of the present invention are useful in polymerisation reactions to form resins from which the polymer supports disclosed in PCT/GB99/02193 can be obtained.

Accordingly, a second aspect of the present invention provides a process for the preparation of a polymer support comprising polymerisation of a monomer comprising a protected hydroxypoly C_{24} alkyleneoxy chain attached to a polymerisable unit wherein the protected hydroxypoly C_{24} alkyleneoxy chain contains from 2 to 10 C_{24} alkyleneoxy groups and wherein the hydroxypoly C_{24} alkyleneoxy chain is protected with an optionally substituted trityl group, under conditions to produce cross-linking.

The monomer comprising a protected hydroxypoly C_{24} alkyleneoxy chain attached to a polymerisable unit wherein the protected hydroxypoly C_{24} alkyleneoxy chain contains from 2 to 10 C_{24} alkyleneoxy groups and wherein the hydroxypoly C_{24} alkyleneoxy chain is protected with an optionally substituted trityl group can be as described above in the first aspect of the present invention.

5 Optionally, in the process of the present invention the monomer comprising a protected hydroxypolyC₂₄ alkyleneoxy chain attached to a polymerisable unit wherein the protected hydroxypolyC₂₄ alkyleneoxy chain contains from 2 to 10 C₂₄ alkyleneoxy groups and wherein the hydroxypolyC₂₄ alkyleneoxy chain is protected with an optionally substituted trityl group may comprise a mixture of isomers.

10 Preferably, when a mixture of isomers is used in the process of the present invention, the monomer is a compound of formula (1). Most preferably, the monomer is a mixture of isomers wherein R⁶O-[C₂₄alkylene-O-]_n group and R¹ occupy isomeric positions on the phenyl ring

15 20 Preferably, in the process of the present invention, the monomer comprising a protected hydroxypolyC₂₄ alkyleneoxy chain attached to a polymerisable unit is copolymerised in the presence of a cross linking monomer.

25 30 The extent of cross linking in the polymers is determined by the concentration of cross linking monomer in the polymerisation reaction. Generally the weight % of cross-linking monomer is in the range of from 0.1 to 70%, commonly from 0.5 to 20%, such as from 1 to 10%, and most preferably no more than 6% by weight. Polymers comprising no more than 20% by weight of cross-linking monomer are generally swellable, whilst polymers comprising greater than 20% of crosslinking monomer are generally not swellable.

35 40 Suitable cross-linking monomers include divinyl benzene (DVB) or multifunctional (meth)acrylates such as di/tri acrylates or di/tri methacrylates such as ethylene glycol diacrylate, ethylene glycol dimethacrylate, trimethylopropane trimethacrylate, trivinylbenzene or N,N'-bis-acryloyl ethylene diamine. Preferably the cross-linking monomer is DVB.

45 50 Preferably 0.5 to 5% by weight of DVB is used. Most preferably 1 to 3% by weight DVB is used.

55 60 Optionally, in the process of the present invention, the monomer comprising a protected hydroxypolyC₂₄ alkyleneoxy chain attached to a polymerisable unit is copolymerised in the presence of one or more monomers selected from styrenes, for example styrene, hydroxystyrene, methylstyrene, hydroxymethylstyrene and chloromethylstyrene, esters of acrylic acid and esters of (meth)acrylic acid, for example methyl acrylate, ethyl acrylate, methyl methacrylate, ethyl acrylate, hydroxyethyl (meth)acrylate and hydroxypropyl (meth)acrylate, and acrylamides, for example N-methyl acrylamide and N-methylol (meth)acrylamide; wherein the phenyl ring in the styrenes is optionally substituted by 1 or 2 substituents often selected from methyl, ethyl, propyl, fluoro, chloro and bromo and wherein hydroxy groups, especially phenolic hydroxy groups, which may be present in the monomers are optionally protected and may subsequently be deprotected.

In a preferred process of the present invention, the monomer comprising a protected hydroxypolyC₂₄ alkyleneoxy chain attached to a polymerisable unit wherein the protected hydroxypolyC₂₄ alkyleneoxy chain contains from 2 to 10 C₂₄ alkyleneoxy groups and wherein the hydroxypolyC₂₄ alkyleneoxy chain is protected with an optionally substituted triyl group is co-polymerised in the presence of one or more cross linking monomers, and one or more monomers selected from styrenes, esters of acrylic acid and esters of (meth)acrylic acid, or acrylamides.

In a highly preferred process of the present invention, the monomer comprising a protected hydroxypolyC₂₄ alkyleneoxy chain attached to a polymerisable unit wherein the protected hydroxypolyC₂₄ alkyleneoxy chain contains from 2 to 10 C₂₄ alkyleneoxy groups and wherein the hydroxypolyC₂₄ alkyleneoxy chain is protected with an optionally substituted triyl group is co-polymerised in the presence of DVB and styrene.

When the polymer support is produced by polymerisation of a mixture of monomers comprising the monomer comprising a protected hydroxypolyC₂₄ alkyleneoxy chain attached to a polymerisable unit wherein the protected hydroxypolyC₂₄ alkyleneoxy chain contains from 2 to 10 C₂₄ alkyleneoxy groups and wherein the hydroxypolyC₂₄ alkyleneoxy chain is protected with an optionally substituted triyl group, and one or more monomers selected from styrenes, esters of acrylic acid and esters of (meth)acrylic acid, or acrylamides, the weight percentage of the monomer comprising a protected hydroxypolyC₂₄ alkyleneoxy chain attached to a polymerisable unit of the total weight of the monomers present is preferably in the range of from 1-99%, more preferably in the range of from 5-80% and most preferably from 15% to 70%.

The process of the present invention is preferably carried out by aqueous suspension polymerisation. The monomers are suspended as droplets (1-1000 μ m) in water. Stabilisers are usually added to prevent agglomeration of the droplets, for example polyvinyl alcohol, polyacrylic acid, polyvinyl pyrrolidone, polyalkylene oxide, barium sulphate, magnesium sulphate or sodium sulphate. The suspension is also normally stirred to maintain the suspension.

Optionally, organic non-water miscible solvents may be used in the polymerisation process. Organic non-water miscible solvents may assist droplet formation in aqueous suspension polymerisation, or may act as porogens.

Optionally inorganic salts may be added to the aqueous phase in aqueous suspension polymerisation. Inorganic salts may assist droplet formation by suppressing monomer solubility in the aqueous medium.

A free radical initiator is preferably used to initiate polymerisation. The type of initiator will generally be selected based on the monomers used. Examples of preferred free radical initiators include benzoyl peroxide, dioctanoyl peroxide, 2,2'-azobisisobutyronitrile and 2,2'-azobis(2,4-dimethylvaleronitrile).

Polymerisation is typically assisted by heating the mixture in the range of 15°C to 160°C, preferably 50°C to 90°C. It will be recognised that the temperature to which the mixture can be heated depends upon the type of monomer and initiator employed.

5 The resultant polymer may then be washed with suitable solvents such as tetrahydrofuran, methanol and water, dried and bead size classified, for example, by sieving.

10 Accordingly a further aspect of the present invention provides a polymer support which comprises protected hydroxypolyC₂₄ alkyleneoxy chains attached to a cross-linked polymer wherein the protected hydroxypolyC₂₄ alkyleneoxy chain contains from 2 to 10 C₂₄ alkyleneoxy groups and wherein the hydroxypolyC₂₄ alkyleneoxy chains are protected with an optionally substituted trityl group.

Preferably, the polymer support of the present application is obtainable by the process of the second aspect of the present invention.

15 The invention, in its broadest aspect, relates to the particular polymer supports however prepared.

The optionally substituted trityl group may subsequently be removed to give the cross-linked polymer containing free hydroxy groups.

20 Methods appropriate for removal of the optionally substituted trityl group include, for example, acid- hydrolysis. Commonly a mixture of trifluoroacetic acid in methylene chloride can be employed. The reader is referred to Advanced Organic Chemistry, 4th Edition, by Jerry March, published by John Wiley & Sons 1992, for general guidance on reaction conditions and reagents.

25 Preferably, when the protecting groups are removed the resulting polymer support has from about 0.1 to about 6 meq free hydroxy groups per gram of polymer.

Cross-linked polymers containing a free hydroxy group are usually produced as beads which range in size from 10µm to 2000µm. Preferably the bead size is from 50µm to 1000µm and most preferably from 75µm to 600µm. The cross-linked polymer beads are generally produced by an aqueous suspension polymerisation process, for example see Journal of Applied Polymer Science, 1982, 27, 133-138, Incorporated herein by reference.

30 The polymer support obtained when the protecting groups are removed from the support according to the present invention has a hydroxy functionality of from 0.1 to about 5, for example up to 4.8 meq (milliequivalents) of hydroxy per gram of polymer, and often from 0.5 to 3.5, commonly 1.0 to 3.3 meq per gram for example from 1.5 to 3 meq per gram of polymer. In many embodiments, the polymer support obtained when the protecting groups are removed have from 0.5 to 2 meq of hydroxy per gram of polymer.

35 The invention will now be described, without limitation, by the following examples in which, unless otherwise stated:-

a) FT-IR spectra were obtained using swollen gels in dichloromethane held between sodium chloride plates, and an ATI Genesis (Matteson) spectrometer.

b) ^{13}C magic angle (MAS) NMR spectra were obtained using solvent swollen gels in the rotor of a Bruker MAS probe on a 400MHz NMR spectrometer.

c) yields are given for illustration and are not necessarily the maximum attainable.

d) the following abbreviations have been used: THF = tetrahydrofuran, DMF = N,N-dimethylformamide, FMOC = fluorenylmethoxycarbonyl, PEG = polyethyleneglycol and THP = tetrahydropyran.

Examples

Preparation of trityl-tetraethyleneglycoxystyrene

STAGE 1

Tetraethyleneglycol (174g, 0.9mol) was placed in a 3 necked round bottom flask fitted with a thermometer and reflux condenser. Pyridine (11cm³, 0.135mol) was added to the mixture stirred. Triphenylmethylchloride (25g, 0.09mol) was dissolved in toluene (30cm³) and this solution was added slowly to the mixture. The mixture was heated to 50°C and the temperature maintained for 1h.

The mixture was allowed to cool and toluene (200cm³) was added to the flask. The solution was extracted with water (500cm³). The aqueous phase was back extracted with toluene (2 x 100cm³). The organic layers were combined and washed with water (2 x 100cm³), dried over MgSO₄ and filtered. The toluene was removed by evaporation under reduced pressure to yield a pale yellow oil (yield 38.5g, 98% based on trityl).

STAGE 2

Mono(trityl)tetraethyleneglycol (30g, 0.069mol), 4-toluenesulfonyl chloride (14.4g, 0.076mol) and dry tetrahydrofuran (50cm³) were placed in a 3 necked round bottom flask fitted with a thermometer and reflux condenser. The flask was placed in a dry-ice bath and the mixture allowed to cool to ~ -20°C. A solution of KOH (25.2g, 0.45mol) in water (100cm³) was added drop-wise over a period of 1h whilst maintaining the temperature at <0°C. Following the addition the reaction mixture was stirred for 1h whilst allowing the solution to warm to ambient.

The solution was extracted with diethylether (3 x 150cm³). The ether layer was dried over MgSO₄, filtered and evaporated under reduced pressure. The solid was washed with MeOH and dried under vacuum (yield 34.3g, 85%).

5 **STAGE 3**

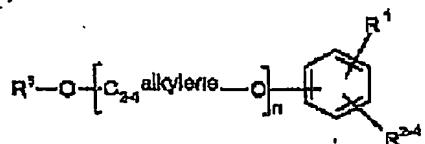
10 NaOMe (0.56g, 10.2mmol) was dissolved in the minimum amount of N,N-dimethylformamide (DMF) and added to 4-acetoxystyrene (1.3cm³, 8.5mmol) contained in a round bottom flask. This solution was stirred at ambient for 45min then a solution of the tosyl derivative of mono(trityl)tetraethyleneglycol (6g, 8.5mmol) in DMF was added. The reaction was allowed to continue overnight at ambient.

15 The DMF was removed by evaporation under reduced pressure. The oil remaining was dissolved in Isopropylacetate and extracted with water. The organic layers were combined, dried over MgSO₄ and filtered. The solvent was removed by evaporation under reduced pressure to leave a pale yellow oil that crystallised on standing (yield 3.5g, 77%).

CLAIMS

1. A monomer which comprises a protected hydroxypolyC₂₄ alkyleneoxy chain attached to a polymerisable unit wherein the protected hydroxypolyC₂₄ alkyleneoxy chain contains from 2 to 10 C₂₄ alkyleneoxy groups and wherein the hydroxypolyC₂₄ alkyleneoxy chain is protected with an optionally substituted trityl group.

2. A monomer of formula (1)



wherein

R¹ is an optionally substituted ethylene group;

R²⁴ are independently hydrogen, hydrocarbyl, halogen, or hydrocarbyloxy;

R⁶ is an optionally substituted trityl group; and

n is 2 to 10.

3. A process for the preparation of a polymer support comprising polymerisation of a monomer comprising a protected hydroxypolyC₂₄ alkyleneoxy chain attached to a polymerisable unit wherein the protected hydroxypolyC₂₄ alkyleneoxy chain contains from 2 to 10 C₂₄ alkyleneoxy groups and wherein the hydroxypolyC₂₄ alkyleneoxy chain is protected with an optionally substituted trityl group, under conditions to produce cross-linking.

4. A polymer support which comprises protected hydroxypolyC₂₄ alkyleneoxy chains attached to a cross-linked polymer wherein the protected hydroxypolyC₂₄ alkyleneoxy chain contains from 2 to 10 C₂₄ alkyleneoxy groups and wherein the hydroxypolyC₂₄ alkyleneoxy chains are protected with an optionally substituted trityl group.

5. A polymer support obtainable by the process of Claim 3.

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- BLACK BORDERS**
- IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- FADED TEXT OR DRAWING**
- BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- SKEWED/SLANTED IMAGES**
- COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- GRAY SCALE DOCUMENTS**
- LINES OR MARKS ON ORIGINAL DOCUMENT**
- REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.